AF

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/346,794	07/02/1999	TERRY P. SNUTCH	NMEDP001-2	2888

25225 7590 11/29/2005

MORRISON & FOERSTER LLP
12531 HIGH BLUFF DRIVE
SUITE 100
SAN DIEGO, CA 92130-2040

EXAMINER	
BASI, NIRMAL SINGH	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 11/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/346,794
Filing Date: July 02, 1999
Appellant(s): SNUTCH ET AL.

Kate H. Marashige
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 9/15/05 appealing from the Office action mailed 1/25/05.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is incorrect. The claims that are rejected and appealed are 25-31, 34 (original 32), 37 (original 35) and 40 (original 38).

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Williams et al, Structure and Functional Expression of Alpha1, Alpha2, and Beta Subunits of a Novel Human Neuronal Calcium Channel Subtype, January 1992, Neuron, Vol. 8, pages 71-64

Ertel et al, Low-voltage-activated T-type Ca2+ Channels, February 1997, TIPS, Vol. 18, pages 37-42

Karp et al., Editorial, Bioinformatics, 1998, Vol. 14, No. 9, pages 753-754

Bork et al., Sequences and Topolgy Deriving biological Knowlwdge from genomic sequences, 1998, current Opinion in structural Biology, Vol. 8, pages 331-332

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 25-31, 34 (original claims 32), 37 (original claim 35) and 40 (original claim 38) are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility.

The claims are directed to identifying compounds which behave as agonists and antagonists for a T-type calcium channel, wherein said calcium channel is encoded by a nucleic acid that hybridizes under specified hybridization conditions to the nucleic acid comprising the nucleic acid of SEQ ID NO:23. The specification, pages 25-26 and Figs. 1-4, disclose the waveforms and current voltage relationships (voltage dependent deactivation, steady state inactivation) of cells transformed with the cDNA of SEQ ID NO:23. There is no disclosure of even a single agonist that stimulates channel activity or an antagonist that reduces channel activity. The question is, if a compound is found to interact with the T-type ion channel of SEQ ID NO:23 what physiological function will

it have? What disease will it treat. It may not treat any disease. The T-type calcium channel of SEQ ID NO:23 has no known utility. There is no disclosure in the specification of any agonists or antagonists of pharmacological significance that have been shown to specifically bind and modulate calcium flux through the T-type calcium channel of SEQ ID NO:23. therefore, further experimentation is required to determine the utility of said T-type ion channel and the effectiveness of the compounds identified by use of said T-type ion channel. It must be noted that just because a compound affects the T-type ion channel does not mean it is likely to treat a disease or even be useful. There is no disclosure that agonists for the T-type ion channel of SEQ ID NO:23 will be beneficial for a particular dysfunction. There is no disclosure which shows that an antagonist will be beneficial. There is no disclosure which shows that an agonist will be beneficial. Both agonists and antagonists may be useless in treatment of a disease. The T-type ion channel of SEQ ID NO:23 may be an integral polypeptide required for normal functioning of the cell. Therefore interfering with its activity may be detrimental to the cell. In that case all agonists and antagonists may be useless for manipulation of said ion channel. The specification discloses conditions associated with calcium channels are namely epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome and Parkinson's disease. As such, agonists or antagonists identified by the claimed methods may be used to treat such conditions. The statement that disease states such as epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome and Parkinson's

disease can be associated with calcium channels may be true but the question is what specific disease state is associated with dysfunction of the ion channel of SEQ ID NO:23. No one calcium channel has been identified that results in all of the diseases disclosed on page 9. The specific dysfunction associated with T-type ion channel of SEQ ID NO:23 is not known or disclosed in the prior art. Therefore what is the utility for a compound that is an antagonist or agonist for said channel. Are agonists beneficial or detrimental for treating a disease condition. Are antagonists beneficial or detrimental for treating a disease condition. Is increased activity of the channel beneficial? Is decreased activity of the channel beneficial? The specification provides no answers with regard to the T-type ion channel of SEQ ID NO:23. Therefore further experimentation is required to assign a utility to the ion channel. Also further experimentation is required assign a utility to any compound than may be shown to be an agonist or antagonist of T-type ion channel of SEQ ID NO:23. Determining which compounds interact with T-type ion channel of SEQ ID NO:23 does not provide a utility for the ion channel or the method of its use, it is just a method to discover the functionality of the ion channel. Further the not evena single compound has been isolated by the claimed method that treats a specific disease or one that has a pharmacological use.

It has been argued that agonists and antagonists identified by the methods of the invention are useful as having an effect on the activity of calcium ion channels. In turn, such agonists and antagonists are useful in treating conditions identified in the specification. Ethanol in increasing concentrations will antagonize the flow of calcium

though the T-type ion channel of SEQ ID NO:23. To follow the argued line of thinking, ethanol therefore must be useful for treating conditions identified in the specification. The conditions identified in the specification are epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome and Parkinson's disease. The examiner is not aware of any art that even remotely suggests that ethanol will treat epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina.

Compounds identified by claimed method are not directly useful but require further experimentation to establish their utility because the ion channel of SEQ ID NO:23 itself has no utility. Agonists and antagonists identified by the methods of the invention are only useful in showing they have an effect on a protein with no known patentable utility. It has been shown Ni^{2+} blocks T channels, but as stated by Sylvie Ertel (page 37, column 3), "It is difficult to predict the actual potency of Ni^{2+} block and it is risky to rely on it to classify an expressed channel as T-type. Since Ni^{2+} blocks T channels, it may block T-type calcium channel of SEQ ID NO:23, if it does then does it mean that it (antagonist) will be useful in treating all the conditions identified in the specification?

There is no showing in the prior art or specification that agonists and antagonists identified by the claimed screening assays are useful for treating diseases including, epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome, and Parkinson's disease. Although the T-type calcium ion channel of SEQ ID NO:23 may be involved in one or more of the

aforementioned disease states further experimentation is required to determine which disease state, if any, is a result of said T-type calcium ion channel dysfunction. Just because a nucleic acid hybridizes to the polynucleotide of SEQ ID NO: 23 it does not automatically mean it will encode a protein that will be involved in the aforementioned disease states. Again further experimentation is required to determine a function. Further, there is no disclosure of even a single agonist or antagonist identified by claimed method that will act as an antagonist or agonist to treat the diverse diseases claimed as possible targets. There is no disclosure of whether an agonist as compared to an antagonist will treat a specific disease. Therefore, further experimentation is required to find a compound that will bind to the T-type calcium ion channel used in instant methods and correlate it with a disease state. Claims 25-27 are directed to method for identifying agonists for a T-type calcium channel. Applicants have not disclosed a single agonist that has been identified by claimed method. Also the art provided by Applicants does not disclose a single compound that behaves as an agonist in the claimed method. Applicants have relied only on antagonists to argue utility.

Prior art does not disclose a utility for claimed invention, it argues to the contrary. The biophysical and pharmacological properties of T-type calcium channels are varied and their function is unknown. Although, the claimed method for identifying agonists and antagonists is considered useful by the Applicants, under 35 U.S.C. 101, they are not considered to have utility. What is the utility for method for identifying agonist and antagonist for a T-type α_1 subunit whose biophysical and pharmacological properties and function is unknown? The critical feature of the invention is the identification of

compounds that activate or inhibit specific α_1 subunits of T-type Ca^{2+} channels. Since the α_1 subunits of T-type Ca^{2+} channels encoded by the polynucleotide of SEQ ID NO: 23 or ion channel encoded by a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO: 23 are not considered to have utility under 35 U.S.C. 101, the method of their use is also are not considered to have utility.

The state of the prior art is disclosed in the review article of Sylvie Ertel et al (Sylvia et al, 1997, TIPS, Vol. 18, pages 37-42). Sylvie Ertel states, "Among Ca^{2+} channels, the low-voltage-activated T-type Ca^{2+} channel (T channel) is probably the most atypical. It was first described in 1984 and is found in a variety of cells where its precise role remains to be established. In addition, its molecular structure has never been defined, despite numerous attempts to sequence and clone it", page 37, first column. Sylvie Ertel does acknowledge that new drugs are being developed, which may block T-type channels. The drugs tested so far have not been shown to treat a single disease state, let alone the laundry list of diseases cited by applicants. Sylvie Ertel discloses the electrophysiological and pharmacological properties of T-type channels are varied (Table 1), and all T channels rarely meet the electrophysiological criteria (page 37, column 2). The effect of compounds on the ion channel is extremely dependent not only on the alpha-subunit but also on that of the associated beta-subunits (Sylvie Ertel et al, page 37, column 3). Therefore, the actions of compounds on T-type calcium channels depend on the molecular composition of the expressed channels and on the experimental conditions (Sylvie Ertel et al, page 37, column 3). The associated beta or other subunits required for a specific function of the T-type

channel protein encoded by the nucleic acid of SEQ ID NO: 23 and the ion channels encoded by a nucleotide, which hybridizes to the nucleic acid of SEQ ID NO: 23, in claimed method, are not disclosed. A compound that acts as an agonist or antagonist on the $\alpha 1$ T-type channel protein used in claimed method may not have the same effect on other $\alpha 1$ T-type channel proteins. For example Ni^{2+} blocks T channels, but as stated by Sylvie Ertel (page 37, column 3), "It is difficult to predict the actual potency of Ni^{2+} block and it is risky to rely on it to classify an expressed channel as T-type. Sylvie Ertel also discloses, many antagonists have been discussed as possible pharmacological markers of T channels (tetrandrine, ethosuximide, phenytoin, zonisamide, U920320) but none are selective or potent enough to be useful (page 38, column 2). Many drugs may block calcium channels but none are available that are selective in blocking T channels (Sylvie Ertel et al, page 38, column 3). Further, compounds may have different effects depending on their concentration. For example, Sylvie Ertel discloses the effect of different Ca^{2+} channel antagonists and states, "Nifedipine (<100 nm) increased aldosterone secretion while higher concentrations reduced it". Other agents that have been shown to interact with T-type channels are mibefradil, Mg^{2+} and Ni^{2+}. Although the claimed method can identify agents that may enhance or reduce the flow of ions into a cell expressing the α_1 subunit of a functional T-type calcium ion channel, neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the disclosed result. For example there is no disclosure that Mg^{2+} or Ni^{2+} can treat epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton

syndrome, and Parkinson's disease associated with interfering with ion channel activity of the α_1 subunit of a functional T-type calcium ion channel. Further there is no disclosure if agonists would be beneficial for treatment of a dysfunction associated with α_1 subunit of T-type calcium ion channel or if antagonists would be beneficial for treatment of said dysfunction. There is no data showing that the ion channel of SEQ ID NO:23 interacts with anyone of the following calcium channel modulators: mibefradil, Nifedipine, tetrandrine, ethosuximide, phenytoin, zonisamide, U920320)Mg^{2+} and Ni^{2+}. Also, the prior art teaches that the entry of calcium through voltage-dependent Ca^{2+} channels in neurons controls diverse functions, such as neurotransmitter release, excitability, and differentiation (Williams et al, 1992, Neuron, Vol. 8, see page 71, column 2). Other diverse effects of compounds on Ca^{2+} channels are disclosed throughout the Review Article of Sylvie Ertel.

The utilities asserted by Applicant are not substantial or specific. Neither the specification nor the art of record disclose any disease states treatable by the agonists and antagonists identified by the method of instant invention. Similarly, neither the specification nor the art of record disclose any instances where blocking any effects of T-type calcium ion channel encoded by the polynucleotide of SEQ ID NO: 23 or ion channel encoded by a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO: 23 would reduce the effect of a disease state. Thus the corresponding asserted utilities are essentially methods of treating unspecified, undisclosed diseases or conditions, which does not define a "real world" context of use. Treating an unspecified, undisclosed disease or condition would require or constitute carrying out further

research to identify or reasonably confirm a "real world" context of use, especially, when the $\alpha 1$ subunit of the T-type calcium channel encoded by the a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO: 23 of the claimed invention is not known. Since neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the T-type calcium channel of SEQ ID NO: 23 or agonists/antagonists identified by claimed method further experimentation is necessary to attribute a utility for the method of using the disclosed T-type calcium ion channel encoded by the polynucleotide of SEQ ID NO:23. See Brenner v. Manson, 383 U.S. 519, 535□36, 148 USPQ 689, 696 (1966) (noting that Congress intended that no patent be granted on a chemical compound whose sole utility consists of its potential role as an object of use-testing, and stated, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."). Since the utilities asserted by Applicant for the T-type calcium ion channel encoded by the polynucleotide of SEQ ID NO: 23, or ion channel encoded by a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO: 23, are not substantial or specific, then it follows that the method of claims 25-31, 34, 37 and 40 (method of identifying compounds capable of acting as agonists or antagonists for T-type mammalian calcium channels), also has no utility. No specific disease state has been shown to result from dysfunction of the T-type calcium ion channel encoded by the polynucleotide of SEQ ID NO: 23, or ion channel encoded by a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO: 23. Similarly, agonists and antagonists identified by said method have no utility in treatment of disease that result from

dysfunction of the T-type calcium ion channel encoded by the polynucleotide of SEQ ID NO: 23, or ion channel encoded by a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO: 23.

A utility to T-type calcium ion channel encoded by the polynucleotide of SEQ ID NO: 23, or ion channel encoded by a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO: 23, cannot be assigned without knowledge of what disease is associated with ion channel dysfunction or what drugs/ligands effect a specific function associated with said dysfunction. The super family of calcium ion channels is highly divergent in their effects and compound specificity. The utility of α_1 subunits T-type Ca^{2+} channels of instant invention cannot be implicated solely from homology to known ion channels or their protein domains. The art does not provide any teaching stating that all members of the family calcium ion channels must have the same effects, the same ligands and be involved in the same disease states. The art discloses evidence to the contrary. The specification has used protein domains/homology are predictive as to the activity of the protein. The utility of claimed α_1 subunits T-type Ca^{2+} channels cannot be implicated solely from homology to known ion channels or their protein domains because the art does not provide any teaching stating that all members of the family of ion channels must have the same effects, the same ligands, transport the same compound and be involved in the same disease states. The art discloses evidence to the contrary (see above).

Bork (Nature Genetics, Vol. 18, pages 313-318, 1998) provide a review article disclosing the problems of using homology detection methods to assigning function to

related members of a family. Bork discloses: a) "While current homology detection methods can cope with data flow, the identification, verification and annotation of functional features need to be drastically improved", page 313, column 1, Abstract, b) there are two bottle necks that need to be overcome en route to efficient functional predictions from protein sequences, i.e., "First, there is the lack of a widely accepted, robust and continuously updated suite of sequence analysis methods integrated into coherent and efficient prediction system. Second, there is considerable 'noise' in the presentation of experimental information, leading to insufficient or erroneous function assignment in sequence databases", page 313, column 1, third paragraph, c) "In-depth analysis of protein sequences often results in functional predictions not attained in the original studies", page 313, column 2, last paragraph, d) "However, more often than not, it is clear that the cellular role of the protein in question differs from that of the detected homologue(s) and there is currently no automatic means to establish how much functional information can be legitimately transferred by analogy from homologue to the query", page 315, column 2, last paragraph, e) pertaining to predictions of protein function, "Do not simply transfer functional information from the best hit. The best hit is frequently hypothetical or poorly annotated; other hits with similar or even lower scores may be more informative; even the best hit may have a different function", while "many proteins are multi-functional; assignment of a single function, which is still common in genome projects, results in loss of information and outright errors" and "It is typical that the general function of a protein can be identified easily but the prediction of substrate specificity is unwarranted; for example, many permeases of different specificity show

approximately the same level of similarity to each other", page 316. Karp (Bioinformatics, Vol. 14, No.9, pages 753-754, 1998) has disclosed the problems of using functional prediction based on homology analysis. Karp states, a) "Although we know the accuracy with which sequence homologs can be determined, we know little about the accuracy of the overall process of assigning function by homology, page 753, column 2, second paragraph, b) "We have more faith in the correctness of those sequences whose functions we determined experimentally, rather than through computational means, page 753, column 2, last paragraph, c) "research is required to estimate the error rate of functional annotation by different methods of computational sequence analysis", page 754, column 2, last paragraph. Bork (Current Opinion in Structural Biology, Vol. 8, pages 331-332, 1998), discusses the problems with deriving biological knowledge from genomic sequences and states, "structural similarity does not lead to iron-clad functional predictions" page 331, column 2 last paragraph, "Structural similarity does not necessarily mean a common evolutionary origin" page 332, column 1, second paragraph, and "Today, what we predict from sequences is at best fragmentary and qualitative", page 332, column 2, second paragraph. Therefore, references discussed above disclose the unpredictability of assigning a specific function to a particular protein based on homology, especially one that belongs to the family of Ca^{2+} channels, which have very different ligand specificity and functions.

Further, the α_1 subunit encoded by nucleotide sequences that hybridize to a nucleic acid comprising SEQ ID NO: 23 may be full-length subunits. The specification does not teach a person of ordinary skill in the art how to use the specified α_1 subunit in

screening assays so that they meet the utility requirements under 35 U.S.C. 101, as indicated above. The specification also does not teach a person of skill in the art how to use the specified α_1 subunit in screening assays so that they meet "how to use" requirement under 35 U.S.C. 112, first paragraph.

Publications at the time the priority application was filed do not demonstrate the α_1 subunit encoded by nucleotide sequences that hybridize to a nucleic acid comprising SEQ ID NO: 23 had a well-established utility, and there was no showing of a single agonists or antagonists that interacted with all T-type calcium channel of SEQ ID NO:23. Also there was no showing all agonists and antagonists, or even one could be used to treat diseases of hypertension, stroke, epilepsy, heart disease and cancer.

The declaration submitted by Dr. Snutch, has been fully considered by the Office, but it does not demonstrate the claimed screening methods are useful for identifying molecules that treat specific T-type calcium channel related diseases. Snutch discloses that abnormal t-type activity is associated with a number of cardiac conditions and that the involvement in a particular condition may depend on its tissue distribution, for instance. It is argued that agonists and antagonists identified with regard to any T-type channel would be useful in any and all of these conditions. Further agued is that the pattern of similar binding among T-type channels can be analogized to such a pattern among L-type channels, all of the T-type channels have similar behaviors. The declaration submitted by Dr. Snutch, has been fully considered but not found persuasive. A compound that acts as an agonist or antagonist on the α1 T-type channel protein used in claimed method may not have the same effect on other α1 T-type

channel proteins. For example as disclosed above, Ni^{2+} blocks T channels, but it is difficult to predict the actual potency of Ni^{2+} block and it is risky to rely on it to classify an expressed channel as T-type. Sylvie Ertel discloses, many antagonists have been discussed as possible pharmacological markers of T channels (tetrandrine, ethosuximide, phenytoin, zonisamide, U920320) but none are selective or potent enough to be useful. Many drugs may block calcium channels but none are available that are selective in blocking T channels (Sylvie Ertel et al, page 38, column 3). Further, compounds may have different effects depending on their concentration. For example, Sylvie Ertel discloses the effect of different Ca^{2+} channel antagonists and states, "Nifedipine (<100 nm) increased aldosterone secretion while higher concentrations reduced it". Although the claimed method can identify agents that may enhance or reduce the flow of ions into a cell expressing the α_1 subunit of a functional T-type calcium ion channel, neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the disclosed result. For example there is no disclosure that Mg^{2+} or Ni^{2+} can treat epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome, and Parkinson's disease associated with interfering with ion channel activity of the α_1 subunit of a functional T-type calcium ion channel. Further there is no disclosure if agonists would be beneficial for treatment of a dysfunction associated with α_1 subunit of T-type calcium ion channel or if antagonists would be beneficial for treatment of said dysfunction. There is no data showing that the ion channel of SEQ ID NO:23 interacts with anyone of the following calcium channel

modulators: mibefradil, Nifedipine, tetrandrine, ethosuximide, phenytoin, zonisamide, U920320, Mg^{2+} and Ni^{2+}. Also, the prior art teaches that the entry of calcium through voltage-dependent Ca^{2+} channels in neurons controls diverse functions, such as neurotransmitter release, excitability, and differentiation (Williams et al, 1992, Neuron, Vol. 8, see page 71, column 2). Other diverse effects of compounds on Ca^{2+} channels are disclosed throughout the Review Article of Sylvie Ertel. For example, if a compound X of unknown function increases calcium flux by the claimed method what is the utility for compound X. What disease will it treat or affect, none is known and none can be predicted based on the assay. Without prior knowledge of the specific known compounds with pharmacological activity that interact with the T-type calcium channel of claimed method it would require further experimentation to assign utility to the claimed method and the T-type calcium channel. There is no disclosure that anyone of the known calcium modulators such mibefradil, Nifedipine, tetrandrine, ethosuximide, phenytoin, zonisamide, U920320, Mg^{2+} and Ni^{2+} interact with the calcium channel used in claimed method.

Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Snutch is an inventor in this application.

Therefore due to the facts delineated above the screening assays do not have a well-established, specific, substantial and credible utility for identifying compounds useful for treating diseases enumerated in the specification. Extensive experimentation is required beyond the claimed processes to identify compounds that treat diseases listed in the specification.

Even if the Office already has allowed Patents directed to T-type channels, said Patents cannot be used to establish utility.

Therefore, the claims are rejected under 35 U.S.C. 101, first paragraph, for reasons provided above.

Claims 25-31, 34 (original claims 32), 37 (original claim 35) and 40 (original claim 38) are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The T-type channel of SEQ ID NO:23 has no utility for reasons given above, therefore the methods of its use have no utility.

(10) Response to Argument

SEO ID NO: 23 Has Been Demonstrated to Encode a Functional T-tvpe alpha1 Subunit

Appellant argues Example 5 discloses a functional alpha 1 subunit of a T-Type calcium channel and a method for determining its functionality. Appellant further argues that the references of Bork and Karp are irrelevant to determing the structure function relationships of the alpha 1 subunit of a T-Type calcium channel. Applicant's arguments have been fully considered but are not found persuasive. The Bork and Karp references were used provide articles disclosing the problems of using homology detection methods to assigning function to related members of a family. The alpha 1

subunit of a T-Type calcium channel of SEQ ID NO:23 belongs to a specific family due to its structure and functional property. How does the skilled artisan make a nucleic acid that will hybridize to the nucleic acid of SEQ ID NO:23 and function with the waveforms and current voltage relationships disclosed in Example 5? As taught by Bork, "It is typical that the general function of a protein can be identified easily but the prediction of substrate specificity is unwarranted". Pertaining to the problems of using functional prediction based on homology analysis Karp states, "Although we know the accuracy with which sequence homologs can be determined, we know little about the accuracy of the overall process of assigning function by homology". Therefore, although the nucleic acid encoding the polypeptide of SEQ ID NO:23 has been classified as an alpha 1 subunit of the T-Type calcium channel family the ligands that modulate are unknown. Appellant is arguing specific functionality, i.e. agonist/ antagonist specificity and involvement in disease states based on structural relationship with other members of the calcium channel family. In fact that is how the alpha 1 subunit of the T-Type calcium channel of instant method was isolated in the first place, based on structural homology to related sequences. Bork and Karp teach that homology is not enough to predict specific function. In instant case Examiner is not arguing that alpha 1 subunit of the SEQ ID NO:23 is not a T-Type calcium channel, based on Applicants disclosure it may be a T-Type calcium channel. The problem is that structural identity and the limited expression data does not disclose the ligand specificity of the calcium channel of claimed method and none is known in the art. The agonists and antagonists for the calcium channel of SEQ ID NO:23 are unknown.

There is no disclosure of another protein with structural similarity and the exact same waveforms and current voltage relationships as alpha 1 subunit of the SEQ ID NO:23 that can be used to predict agonist or antagonist specificity to determine functionality for the ion channel.

The state of the prior art is disclosed in the review article of Sylvie Ertel et al (Sylvia et al, 1997, TIPS, Vol. 18, pages 37-42). Sylvie Ertel states, "Among Ca^{2+} channels, the low-voltage-activated T-type Ca^{2+} channel (T channel) is probably the most atypical. It was first described in 1984 and is found in a variety of cells where its precise role remains to be established. In addition, its molecular structure has never been defined, despite numerous attempts to sequence and clone it", page 37, first column. Sylvie Ertel does acknowledge that new drugs are being developed, which may block T-type channels. The drugs tested so far have not been shown to treat a single disease state, let alone the laundry list of diseases cited by applicants. Sylvie Ertel discloses the electrophysiological and pharmacological properties of T-type channels are varied (Table 1), and all T channels rarely meet the electrophysiological criteria (page 37, column 2). The effect of compounds on the ion channel is extremely dependent not only on the alpha-subunit but also on that of the associated beta-subunits (Sylvie Ertel et al, page 37, column 3). Therefore, the actions of compounds on T-type calcium channels depend on the molecular composition of the expressed channels and on the experimental conditions (Sylvie Ertel et al, page 37, column 3). The associated beta or other subunits required for a specific function of the T-type channel protein encoded by the nucleic acid of SEQ ID NO: 23 and the ion channels

encoded by a nucleotide, which hybridizes to the nucleic acid of SEQ ID NO: 23, in claimed method, are not disclosed. A compound that acts as an agonist or antagonist on the α1 T-type channel protein used in claimed method may not have the same effect on other α1 T-type channel proteins. For example Ni^{2+} blocks T channels, but as stated by Sylvie Ertel (page 37, column 3), "It is difficult to predict the actual potency of Ni^{2+} block and it is risky to rely on it to classify an expressed channel as T-type. Sylvie Ertel also discloses, many antagonists have been discussed as possible pharmacological markers of T channels (tetrandrine, ethosuximide, phenytoin, zonisamide, U920320) but none are selective or potent enough to be useful (page 38, column 2). Many drugs may block calcium channels but none are available that are selective in blocking T channels (Sylvie Ertel et al, page 38, column 3). Further, compounds may have different effects depending on their concentration. For example, Sylvie Ertel discloses the effect of different Ca^{2+} channel antagonists and states, "Nifedipine (<100 nm) increased aldosterone secretion while higher concentrations reduced it". Other agents that have been shown to interact with T-type channels are mibefradil, Mg^{2+} and Ni^{2+}. Although the claimed method can identify agents that may enhance or reduce the flow of ions into a cell expressing the α_1 subunit of a functional T-type calcium ion channel, neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the disclosed result. For example there is no disclosure that Mg^{2+} or Ni^{2+} can treat epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome, and Parkinson's disease associated with interfering with ion channel activity

of the α_1 subunit of a functional T-type calcium ion channel. Further there is no disclosure if agonists would be beneficial for treatment of a dysfunction associated with α_1 subunit of T-type calcium ion channel or if antagonists would be beneficial for treatment of said dysfunction. There is no data showing that the ion channel of SEQ ID NO:23 interacts with anyone of the following calcium channel modulators: mibefradil, Nifedipine, tetrandrine, ethosuximide, phenytoin, zonisamide, U920320)Mg^{2+} and Ni^{2+}. Also, the prior art teaches that the entry of calcium through voltage-dependent Ca^{2+} channels in neurons controls diverse functions, such as neurotransmitter release, excitability, and differentiation (Williams et al, 1992, Neuron, Vol. 8, see page 71, column 2). Other diverse effects of compounds on Ca^{2+} channels are disclosed throughout the Review Article of Sylvie Ertel. Bork (Current Opinion in Structural Biology, Vol. 8, pages 331-332, 1998), discusses the problems with deriving biological knowledge from genomic sequences and states, "structural similarity does not lead to iron-clad functional predictions" page 331, column 2 last paragraph, "Today, what we predict from sequences is at best fragmentary and qualitative", page 332, column 2, second paragraph. Therefore, references discussed above disclose the unpredictability of assigning a specific function to a particular protein based on homology, especially one that belongs to the family of Ca^{2+} channels, which have very different ligand specificity and functions.

Neither Williams nor Ertel Show Lack of Utility

Appellant argues the Williams and Ertel articles are also irrelevant. Appellant argues the Williams reference article does not even pertain to the T-type calcium ion channels

that are the subject of the present invention. Second, while these functions may be "diverse"' all of them relate to enhancing neural activity; thus, to the extent that neural activity should be depressed as, for example, in the case of epilepsy, modulation of these diverse functions would all be desirable in treatment.

Appellant argues Ertel notes several instances where the role of T-type channels in diseases and undesired conditions is clear. Page 41, middle paragraph, notes: "*Another system where a role for T channels is fairly clear is in the generation of rhythmic activity in some neuronal structures: indeed, anticonvulsants are probably the most prolific therapeutic field for*

T-channel blockers".

Appellant's arguments have been fully considered but are not found persuasive. Williams et al teaches that the entry of calcium through voltage-dependent Ca^{2+} channels in neurons controls diverse functions, such as neurotransmitter release, excitability, and differentiation. The reference is drawn to L-type calcium channels. The reference is relevant because as stated in the Declaration of Snutch, "The pattern of similar binding among T-type channels can be analogized to such a pattern among L-type channels, all of the T-type channels have similar behaviors". It follows if functions of L-type channel can be diverse so can the function of the T-type channel.

Pertaining to the quotation from page 41 of Ertel although the role of T channels may be clear in some instances, there is no disclosure to which system the channel of SEQ ID NO:23 belongs and there is also no disclosure of any anticonvulsants that interact as agonists or antagonists with the channel of SEQ ID NO:23.

The state of the prior art is disclosed in the review article of Sylvie Ertel et al (Sylvia et al, 1997, TIPS, Vol. 18, pages 37-42). Sylvie Ertel states, "Among Ca^{2+} channels, the low-voltage-activated T-type Ca^{2+} channel (T channel) is probably the most atypical. It was first described in 1984 and is found in a variety of cells where its precise role remains to be established. In addition, its molecular structure has never been defined, despite numerous attempts to sequence and clone it", page 37, first column. Sylvie Ertel does acknowledge that new drugs are being developed, which may block T-type channels. The drugs tested so far have not been shown to treat a single disease state, let alone the laundry list of diseases cited by applicants. Sylvie Ertel discloses the electrophysiological and pharmacological properties of T-type channels are varied (Table 1), and all T channels rarely meet the electrophysiological criteria (page 37, column 2). The effect of compounds on the ion channel is extremely dependent not only on the alpha-subunit but also on that of the associated beta-subunits (Sylvie Ertel et al, page 37, column 3). Therefore, the actions of compounds on T-type calcium channels depend on the molecular composition of the expressed channels and on the experimental conditions (Sylvie Ertel et al, page 37, column 3). The associated beta or other subunits required for a specific function of the T-type channel protein encoded by the nucleic acid of SEQ ID NO: 23 and the ion channels encoded by a nucleotide, which hybridizes to the nucleic acid of SEQ ID NO: 23, in claimed method, are not disclosed. A compound that acts as an agonist or antagonist on the $\alpha 1$ T-type channel protein used in claimed method may not have the same effect on other $\alpha 1$ T-type channel proteins. For example Ni^{2+} blocks T channels, but as stated

by Sylvie Ertel (page 37, column 3), "It is difficult to predict the actual potency of Ni^{2+} block and it is risky to rely on it to classify an expressed channel as T-type. Sylvie Ertel also discloses, many antagonists have been discussed as possible pharmacological markers of T channels (tetrandrine, ethosuximide, phenytoin, zonisamide, U920320) but none are selective or potent enough to be useful (page 38, column 2). Many drugs may block calcium channels but none are available that are selective in blocking T channels (Sylvie Ertel et al, page 38, column 3). Further, compounds may have different effects depending on their concentration. For example, Sylvie Ertel discloses the effect of different Ca^{2+} channel antagonists and states, "Nifedipine (<100 nm) increased aldosterone secretion while higher concentrations reduced it". Other agents that have been shown to interact with T-type channels are mibefradil, Mg^{2+} and Ni^{2+}. Although the claimed method can identify agents that may enhance or reduce the flow of ions into a cell expressing the α_1 subunit of a functional T-type calcium ion channel, neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the disclosed result. For example there is no disclosure that Mg^{2+} or Ni^{2+} can treat epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome, and Parkinson's disease associated with interfering with ion channel activity of the α_1 subunit of a functional T-type calcium ion channel. Further there is no disclosure if agonists would be beneficial for treatment of a dysfunction associated with α_1 subunit of T-type calcium ion channel or if antagonists would be beneficial for treatment of said dysfunction. There is no data showing that the ion channel of SEQ ID

NO:23 interacts with anyone of the following calcium channel modulators: mibefradil, Nifedipine, tetrandrine, ethosuximide, phenytoin, zonisamide, U920320)Mg^{2+} and Ni^{2+}. Also, the prior art teaches that the entry of calcium through voltage-dependent Ca^{2+} channels in neurons controls diverse functions, such as neurotransmitter release, excitability, and differentiation (Williams et al, 1992, Neuron, Vol. 8, see page 71, column 2). Other diverse effects of compounds on Ca^{2+} channels are disclosed throughout the Review Article of Sylvie Ertel.

Publications at the time the priority application was filed do not demonstrate the α_1 subunit encoded by nucleotide sequences that hybridize to a nucleic acid comprising SEQ ID NO: 23 had a well-established utility, and there was no showing of a single agonists or antagonists that interacted with all T-type calcium channel of SEQ ID NO:23. Also there was no showing all agonists and antagonists, or even one could be used to treat diseases of hypertension, stroke, epilepsy, heart disease and cancer. A compound that acts as an agonist or antagonist on the α1 T-type channel protein used in claimed method may not have the same effect on other α1 T-type channel proteins. For example as disclosed above, Ni^{2+} blocks T channels, but it is difficult to predict the actual potency of Ni^{2+} block and it is risky to rely on it to classify an expressed channel as T-type. Sylvie Ertel discloses, many antagonists have been discussed as possible pharmacological markers of T channels (tetrandrine, ethosuximide, phenytoin, zonisamide, U920320) but none are selective or potent enough to be useful. Many drugs may block calcium channels but none are available that are selective in blocking T channels (Sylvie Ertel et al, page 38, column 3). Further, compounds may have

different effects depending on their concentration. For example, Sylvie Ertel discloses the effect of different Ca^{2+} channel antagonists and states, "Nifedipine (<100 nm) increased aldosterone secretion while higher concentrations reduced it". Although the claimed method can identify agents that may enhance or reduce the flow of ions into a cell expressing the α_1 subunit of a functional T-type calcium ion channel, neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the disclosed result. For example there is no disclosure that Mg^{2+} or Ni^{2+} can treat epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome, and Parkinson's disease associated with interfering with ion channel activity of the α_1 subunit of a functional T-type calcium ion channel. Further there is no disclosure if agonists would be beneficial for treatment of a dysfunction associated with α_1 subunit of T-type calcium ion channel or if antagonists would be beneficial for treatment of said dysfunction. There is no data showing that the ion channel of SEQ ID NO:23 interacts with anyone of the following calcium channel modulators: mibefradil, Nifedipine, tetrandrine, ethosuximide, phenytoin, zonisamide, U920320, Mg^{2+} and Ni^{2+}. Also, the prior art teaches that the entry of calcium through voltage-dependent Ca^{2+} channels in neurons controls diverse functions, such as neurotransmitter release, excitability, and differentiation (Williams et al, 1992, Neuron, Vol. 8, see page 71, column 2). Other diverse effects of compounds on Ca^{2+} channels are disclosed throughout the Review Article of Sylvie Ertel. For example, if a compound X of unknown function increases calcium flux by the claimed method what is the utility for

compound X. What disease will it treat or affect, none is known and none can be predicted based on the assay. Without prior knowledge of the specific known compounds with pharmacological activity that interact with the T-type calcium channel of claimed method it would require further experimentation to assign utility to the claimed method and the T-type calcium channel. There is no disclosure that anyone of the known calcium modulators such mibefradil, Nifedipine, tetrandrine, ethosuximide, phenytoin, zonisamide, U920320, Mg^{2+} and Ni^{2+} interact with the calcium channel used in claimed method. Appellant argues mibefradil, is specific for T channels. Mibefradil has not been shown to bind the calcium channel of SEQ ID NO: 23. In fact mibefradil is not even mentioned in the specification as possible candidate.

The Specification Clearly Describes a Real World Utility

Appellant argues the specification itself identifies conditions for which compounds identified in the claimed method would be candidate therapeutics. These indications are listed on page 9 of the Specification, second 111 paragraphs, as including epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia angina, depression, small cell lung carcinoma, Lambert-Eaton syndrome and Parkinson's disease. The statement that many disease states can be associated with calcium channels may be true but the question is what specific disease state is associated with dysfunction of the ion channel of SEQ ID NO: 23. No one calcium channel has been identified that results in all of the diseases disclosed above. The specific dysfunction associated with T-type ion channel of SEQ ID NO: 23 is not known or disclosed in the

prior art. Therefore what is the utility for a compound that is an antagonist or agonist for said channel? Are agonists beneficial or detrimental for treating a disease condition? Are antagonists beneficial or detrimental for treating a disease condition? Is increased activity of the channel beneficial? Is decreased activity of the channel beneficial? The specification provides no answers with regard to the T-type ion channel of SEQ ID NO: 23. Therefore further experimentation is required to assign a utility to the ion channel. Also further experimentation is required assign a utility to any compound than may be shown to be an agonist or antagonist of T-type ion channel of SEQ ID NO: 23. Determining which compounds interact with T-type ion channel of SEQ ID NO: 23 does not provide a utility for the ion channel or the method of its use, it is just a method to discover the functionality of the ion channel. Further not a single compound has been isolated by the claimed method that treats a specific disease or one that has pharmacological use. The declaration submitted by Dr. Snutch, has been fully considered by the Office, but it does not demonstrate the claimed screening methods are useful for identifying molecules that treat specific T-type calcium channel related diseases. Snutch discloses that abnormal T-type activity is associated with a number of cardiac conditions and that the involvement in a particular condition may depend on its tissue distribution, for instance. It is argued that agonists and antagonists identified with regard to any T-type channel would be useful in any and all of these conditions. Further agued is that the pattern of similar binding among T-type channels can be analogized to such a pattern among L-type channels; all of the T-type channels have similar behaviors. The declaration submitted by Dr. Snutch, has been fully considered but not

found persuasive. A compound that acts as an agonist or antagonist on the α1 T-type channel protein used in claimed method may not have the same effect on other α1 T-type channel proteins. For example as disclosed above, Ni^{2+} blocks T channels, but it is difficult to predict the actual potency of Ni^{2+} block and it is risky to rely on it to classify an expressed channel as T-type. Sylvie Ertel discloses, many antagonists have been discussed as possible pharmacological markers of T channels (tetrandrine, ethosuximide, phenytoin, zonisamide, U920320) but none are selective or potent enough to be useful. Many drugs may block calcium channels but none are available that are selective in blocking T channels (Sylvie Ertel et al, page 38, column 3). Further, compounds may have different effects depending on their concentration. For example, Sylvie Ertel discloses the effect of different Ca^{2+} channel antagonists and states, "Nifedipine (<100 nm) increased aldosterone secretion while higher concentrations reduced it". Although the claimed method can identify agents that may enhance or reduce the flow of ions into a cell expressing the α_1 subunit of a functional T-type calcium ion channel, neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the disclosed result. For example there is no disclosure that Mg^{2+} or Ni^{2+} can treat epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome, and Parkinson's disease associated with interfering with ion channel activity of the α_1 subunit of a functional T-type calcium ion channel. Further there is no disclosure if agonists would be beneficial for treatment of a dysfunction associated with α_1 subunit of T-type calcium ion channel or if antagonists would be

beneficial for treatment of said dysfunction. There is no data showing that the ion channel of SEQ ID NO: 23 interacts with anyone of the following calcium channel modulators: mibefradil, Nifedipine, tetrandrine, ethosuximide, phenytoin, zonisamide, U920320, Mg^{2+} and Ni^{2+}. Also, the prior art teaches that the entry of calcium through voltage-dependent Ca^{2+} channels in neurons controls diverse functions, such as neurotransmitter release, excitability, and differentiation (Williams et al, 1992, Neuron, Vol. 8, see page 71, column 2). Other diverse effects of compounds on Ca^{2+} channels are disclosed throughout the Review Article of Sylvie Ertel. For example, if a compound X of unknown function increases calcium flux by the claimed method what is the utility for compound X? What disease will it treat or affect, none is known and none can be predicted based on the assay. Without prior knowledge of the specific known compounds with pharmacological activity that interact with the T-type calcium channel of claimed method it would require further experimentation to assign utility to the claimed method and the T-type calcium channel. There is no disclosure that anyone of the known calcium modulators such mibefradil, Nifedipine, tetrandrine, ethosuximide, phenytoin, zonisamide, U920320, Mg^{2+} and Ni^{2+} interact with the calcium channel used in claimed method.

Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Snutch is an inventor in this application.

Applicant further go to show the diverse functionality of T-type calcium channels.

The Position of the Examiner Does Not Conform to PTO Guidelines or Federal Circuit Law

Appellant argues it is always true that few, if any, of compounds that are identified in a screen go on successfully actually to treat a condition or disease. Despite these limitations, screening assays are widely used by the pharmaceutical industry at the expense of millions of dollars. If these are so useless, then why are so many pharmaceutical company resources expended on them, and so many resources expended on developing them? Also argued is that the specific dysfunction associated with T-type ion channel of SEQ ID NO:23 is not known or disclosed in the prior art is clearly not relevant, since the specification itself describes these disease states. Appellant further argues that "The Examiner goes on to state that "not a single compound has been isolated by the claimed method that treats a specific disease." Another irrelevant statement especially in view of the fact that evidence of record shows that the T-type channel inhibitor mibefradil is actually in clinical trials for treatment of hypertension." Appellant's arguments have been fully considered but are not found persuasive. Examiner does not know really know why screening assays are widely used by the pharmaceutical industry at the expense of millions of dollars. Presumably assays that are based on methods with a known utility will produce favorable results and others, which are based on assays with no utility, will be a waste of money. In instant case Appellant discloses that it is irrelevant to know specific dysfunction associated with the T-type ion channel of SEQ ID NO:23 since the specification discloses the disease states. The specification discloses many disease states not of which have been shown to be specific to dysfunction or function of the calcium channel of SEQ ID NO:23. Appellant also argues that Examiners statement that "not a single

compound has been isolated by the claimed method that treats a specific disease." Is "Another irrelevant statement especially in view of the fact that evidence of record shows that the T-type channel inhibitor mibefradil is actually in clinical trials for treatment of hypertension." Although mibefradil may be in clinical trials it did no go to said trials by use of claimed assay. There is no disclosure in the prior art or the specification that mibefradil binds the calcium channel of SEQ ID NO:23. Further for the simple reason that mibefradil has gone for clinical trials for the treatment of hypertension goes to show that treatment of epilepsy, migraine, ataxia, schizophrenia, arrhythmia angina, depression, small cell lung carcinoma, Lambert-Eaton syndrome were not viable options. All compounds that bind to calcium channels do not all treat the laundry list of dysfunctions recited in the specification. Although compounds that bind the calcium channel of SEQ ID NO: 23 can be found, what will be their use without knowledge of the functionality of the calcium channel functions.

Further, applicants' reference to issued Patents as establishing a patentable utility for the claimed protein is not persuasive because each application is examined on its own merits. In the decision of *In re Hutchison*, 69 USPQ 138 (CCPA, 1946), the court held that

> We are not concerned, of course, with the allowed claims in either the patent or in this application. The sole question for our determination is whether the six article claims on appeal were properly rejected below, and this we pass upon without further reference to, and without comparing them with, the claims in the patent or the claims, which stand allowed in this application.

In essence, the position in the instant application that each application is examined on its own merits can be found in the judicial precedent cited above. The

rejections in the instant application will only be withdrawn if they are shown to be legally or factually unsound.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Nirmal S. Basi, PhD

Conferees:

Anthony Caputa, PhD

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Brenda Brumback, PhD

BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600